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Application No.10/773,446

NOV 07 2006

Docket No.: 66145(300604)

REMARKS**Status of Application:**

The present amendment is being submitted along with a Request for Continued Examination in response to a final Office Action dated 05/16/06. Entry of the amendment and withdrawal of the finality of the Office Action is respectfully requested. Claims 1-39, 53, 57, 58, and 60 are pending in the application. Claims 14, and 18-52 are withdrawn, subject to a restriction requirement. Claims 1, 2, 10, 11, 14, 15-17, and 53 have been amended. Claims 3, 18-52, 54-56, 59, and 61-62 have been cancelled without prejudice. Therefore, upon entry of the instant amendment, Claims 1, 2, 4-12, 15-17, 53, 57, 58, and 60 will be pending in the application.

Substance of Interview Conducted at USPTO October 24, 2006:

Applicants gratefully acknowledge the personal interview conducted on October 24, 2006, with Examiners Juedes and Ewoldt ("the Interview") at which Applicants' representative, the undersigned, presented two exhibits providing: (1) background on age-related macular degeneration (AMD) and the process of phagocytosis of photoreceptor outer segments by RPE cells of the retina and (2) experimental data pertaining to monkey and mouse models of AMD that overexpress MT1-MMP, described in the subject application. Copies of the exhibits were provided to the Examiners for the record.

Outstanding new matter rejections were first discussed. Applicants' representative first clarified, and Examiner Juedes confirmed, that the outstanding rejections applied only to sections B) and D) of the 35 U.S.C. § 112, first paragraph, written description (new matter) rejections (Office Action, p. 3). The Examiners confirmed that the rejections set forth in sections A) and C) had been overcome by Applicants' previous response filed 02/21/06, although this was not explicitly stated in the Office Action dated 05/16/06. Applicant's representative addressed the remaining rejections set forth in sections B) and D), pointing to support for the alleged new matter in the specification and claims as filed (further addressed *infra* under 35 U.S.C. § 112).

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Next, the rejection of the pending claims under 35 U.S.C. § 102(b) in view of the '440 publication was discussed. The substance of the discussion is included below.

In the Specification:

The paragraphs on pages 19, 20, 21-22, 31 and 40 have been amended to correct an inadvertent clerical error that occurred in the numbering of the amino acid sequences that correspond to the nucleic acid sequences identified as SEQ ID NOS:1-15 (Table 1, pages 19-20) and as SEQ ID NOS:2, 16, 17, 9, 10, and 15 (Table 2, page 21). More specifically, Tables 1 and 2 in the specification as filed incorrectly listed these amino acid sequences as being one number higher than their correct number. For example, the correct amino acid sequences corresponding to SEQ ID NO:1 in Table 1 are SEQ ID NOS:70-78, not 71-79 as listed. Similarly, the respective amino acid sequences corresponding to the nucleic acid sequences of SEQ ID NOS:2-15 in Table 1 are the following: SEQ ID NOS: 79, 80, 81-83, 84, 85, 86, 87, 88, 89, 90, 91-97, 98, 99, and 100, whereas these numbers are all higher by one number in Table 1 as filed. For example, the correct sequence identifier for the human MT1-MMP amino acid sequence encoded by SEQ ID NO:15 is SEQ ID NO:100, not 101 as shown in Table 1.

It is important to note that this is not new matter. Support for this amendment can be found, for example, by reviewing the sequence listing of the subject application. For instance, SEQ ID NO:15 is a 2365-base DNA sequence corresponding to human MT1-MMP nucleic acid sequence, and SEQ ID NO:100 is a 582-amino acid human MT1-MMP protein sequence encoded by SEQ ID NO:15. This can be verified by comparing the nucleic acid and amino acid sequences, as listed in the sequence listing, with the corresponding human MT1-MMP DNA and protein sequence data available, e.g., in GenBank. Furthermore, the error is readily apparent by reviewing SEQ ID NO:101 in the sequence listing, as but one example. SEQ ID NO:101 is a 2285-amino acid sequence. Those of ordinary skill in the art of molecular biology would immediately recognize the error because a 2365-base nucleic acid sequence (SEQ ID NO:15) cannot encode a 2285-amino protein sequence (SEQ ID NO:101). In fact, SEQ ID NO:101 is an amino acid sequence of human SW1-SNF related/OSA-1 nuclear protein

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(see Table 2, p. 21), corresponding to the 8595-base DNA sequence shown as SEQ ID NO:16.

Applicants sincerely regret the inadvertent clerical error that resulted in the incorrect identification in the specification of several of the amino acid sequences, as discussed, and respectfully request entry of the amended paragraphs to correct these errors in order to accurately identify the sequences.

In the Claims:

Claims 1, 2, 13, 15, and 16 have been amended to recite a single AMDP- or phagocytosis-related gene (i.e., MT1-MMP), or the sequence identifier (i.e., SEQ ID NO:15) corresponding to human MT1-MMP nucleic acid sequence. Support for the amendments can be found in the specification and claims as originally filed. Additionally, Claim 2 has been amended to more clearly describe the MT1-MMP gene as comprising "a nucleic acid sequence encoding" human MT1-MMP protein, consistent with the recitation of Claim 53. Claim 14, although withdrawn due to a restriction requirement, is linked to Claim 1 and will be rejoined if generic Claim 1 is found allowable (Office Action dated 07/11/05, page 7, §3). Support for the amendment of Claim 14 can be found, for example, in the specification at page 31, lines 27-31 and at page 32, lines 28-31. No new matter has been added.

Corrected Form PTO/SB/08A

In response to the request (Office Action, page 3, item 3) regarding Reference S in the Information Disclosure Statement (IDS) filed April 1, 2005, Applicants respectfully submit herewith a replacement of the Form PTO/SB/08A that recites the information requested in the Office Action dated October 21, 2005. The requested information was previously provided to the Examiner in the amendment filed February 21, 2006.

Rejections Under 35 U.S.C. § 112:

Applicants acknowledge with gratitude the withdrawal of the rejection of Claims 1-12 and 53, 57-58 and 60 under 35 USC § 112, second paragraph.

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Applicants further gratefully acknowledge the withdrawal of the rejections of Claims 1-13, 15-17, 53, 54-56 and 57-58, and 60 under 35 USC § 112, first paragraph, as outlined in sections A and C of the Office Action mailed 10/21/05.

Claims 1-13, 15-17, 53, 57-58, and 60 stand rejected under 35 USC § 112, first paragraph, for failure to satisfy the written description requirement (new matter rejection). According to the Office Action (p. 3, second paragraph), the specification and claims as originally filed do not provide support for the invention as now claimed, as outlined in sections B and D of the Office Action mailed 10/21/05. Applicants disagree and respectfully request reconsideration of these rejections in view of the following.

In regard to B), Claim 1 was previously amended to recite the phrase "or protein." The Examiner correctly acknowledges that the specification at page 31 "discloses... that agents can modulate or down-regulate (i.e. decrease) the expression of mRNA or protein of an AMDP-related gene." However, the Office Action goes on to allege that "there does not appear to be a disclosure of delaying disease with an agent that down-regulates or decreases the "activity" of an AMDP-related protein, as now claimed" (emphasis added).

Regarding downregulating the activity of an AMDP-related protein, Applicants respectfully point to specific support in the specification as filed, e.g., on page 31, lines 24-26, and on page 40, lines 15-30 bridging p. 41, line 2, which state as follows (emphasis added):

(p. 31) The inhibitory agents can also include antibody molecules that selectively bind to an over-expressed phagocytosis-related and/or AMDP-related protein, such as PD2S, MT1-MMP or AMDP-3.

(p. 40-41) Other embodiments of agents that can down-regulate expression or neutralize the biological activity of the phagocytosis-related and/or AMDP-related genes of the invention are based on proteins. An example of a protein that can modulate expression and/or neutralize a biological function of a phagocytosis-related and/or AMDP-related gene product is an antibody that specifically binds a phagocytosis-related and/or

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AMDP-related polypeptide or peptide. Preferred polypeptides, for which mRNA levels are shown herein to be elevated in AMD, include those encoded by nucleic acids having SEQ ID NOS:2, 15 and 17, i.e., polypeptides having amino acid sequences respectively identified herein as SEQ ID NOS:79, 100, and 102-120. The antibodies of the invention can be used to interfere with the interaction of a phagocytosis-related and/or AMDP-related protein with one or more molecules that bind or otherwise interact with the phagocytosis-related and/or AMDP-related protein. For instance, an antibody directed against MT1-MMP protein is thought to neutralize the ability of this protein to activate progelatinase A. The results of a study described herein using an antibody directed against MT1-MMP showed delay of retinal degeneration in a rat model of RPE-based disease characterized by over-expression of MT1-MMP. Accordingly, inhibition of excessive production of MT1-MMP in the interphotoreceptor matrix using an anti-MT1-MMP antibody might be used in the eyes of patients with AMD to reduce destruction of the matrix and improve phagocytosis. (Emphasis added.)

In view of these passages, Applicants respectfully submit that there is clear written description in the specification as filed of methods for delaying disease with an agent that down-regulates or decreases the activity of an AMDP-related protein such as MT1-MMP (e.g., decreasing MT1-MMP's biological activity of activating progelatinase A, or degrading extracellular matrix, as recited in original Claims 16 and 17). Thus, this is not new matter. Claim 1 has been amended to recite "an agent that decreases...the activity of an AMDP-related or phagocytosis-related protein." Accordingly, Applicants believe that the rejections of claims 1-13, 15-17, 53, 57-58, and 60 as outlined in section B of the Office Action have been overcome, and respectfully request withdrawal of these rejections. Claims 61-62 having been cancelled, the rejection is moot with regard to these claims.

In regard to section D of the Office Action, claims 58-60 stand rejected for failure to meet the written description requirement, as allegedly containing new matter (Office

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Action, p. 3). In response to Applicants' previous arguments pointing to specific support in the specification for the language used in the claims, the Office Action (p. 4) now states "However, a review of pg. 69 reveals a disclosure of a specific example involving injection of an MT1-MMP antibody into the eye of an RCS rat. This cannot be considered adequate written description for the generic method of the claims, which has a much broader scope than this specific example, since it is drawn to delaying or reversing a retinal or choroidal degenerative disease or condition in any subject." The paragraph ends with the conclusion that "Applicant has only disclosed injecting an MT1-MMP antibody subretinally into the eyes of an RCS rat."

Applicants respectfully traverse this statement, and would like to first direct the Examiner's attention to several passages in the Detailed Description providing clear written description for the claimed method of administering an antibody against MT1-MMP to the eye or subretinal space to delay or reverse a retinal degenerative condition in a human subject (e.g., a patient with AMD), for example:

(p.40, line 27-p. 41, line 2) The results of a study described herein using an antibody directed against MT1-MMP showed delay of retinal degeneration in a rat model of RPE-based disease characterized by over-expression of MT1-MMP. Accordingly, inhibition of excessive production of MT1-MMP in the interphotoreceptor matrix using an anti-MT1-MMP antibody might be used in the eyes of patients with AMD to reduce destruction of the matrix and improve phagocytosis.

(p. 54, lines 16-23 and 26-29) Significantly, following injection of an anti-MT1-MMP antibody (2 μ l volume) into the subretinal space of 7-day old RCS rats, the rate of photoreceptor degeneration relative to controls, is markedly slowed in anti-MT1-MMP antibody-injected animals observed at 30 and 60 days of age, whereas control antibodies or sham injection have no effect (FIG. 14). These results provide evidence that an agent directed against MT1-MMP protein present in the outer retina, for example within the interphotoreceptor matrix in the subretinal space, can provide a

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beneficial effect, such as slowing or reversing a retinal degenerative condition....Based on the discoveries described herein, it is now apparent that this gene provides an attractive new candidate gene to target therapeutically for AMD and other retinal and choroidal degenerative diseases.

Based on the foregoing, Applicants respectfully submit that the subject matter of Claims 58 and 60 is not new matter, as it was clearly described in the specification and Claims 58 and 60 as originally filed, and accordingly request that the §112 new matter rejection of section D be withdrawn.

Because the rejection of claims 58 and 60 was maintained despite Applicants pointing to specific support in the specification, it would appear that the reference in the Office Action, at page 4, to the breadth of the claims is meant to relate more to a "written description (lack of possession)" rejection under 35 U.S.C. §112, first paragraph.

If, indeed, the rejection of these claims relates more to lack of possession, Applicants respectfully submit that they were indeed in possession of the invention as claimed at the time of filing. The application as filed encompasses much more than a specific example involving an RCS rat. In fact, the RCS rat experiment was used merely as a model to demonstrate proof-of-principle of a therapeutic approach, based on a discovery first made by the inventors in human eyes. More specifically, as explained by the undersigned in the Interview, and described in the specification, a body of discovery relating to MT1-MMP overexpression in human AMD preceded the use of an animal model for testing of therapeutic agents. In brief, Applicants' specification discloses that Applicants discovered that eyes of three types of animal subjects with retinal degenerations, i.e., 1) humans with AMD, 2) monkeys with AMD and 3) RCS rats with RPE-based retinal degeneration all over-express MT1-MMP (see, for example, Summary of the Invention, p. 7, lines 8-13, and Detailed Description, page 54, lines 1-2).

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As summarized below and described in the Examples, data from human AMD-diseased tissue (eyebank eyes) was generated first; whereas data from animal models was generated secondarily for confirmation of results obtained from the human samples. To briefly recapitulate, a central discovery of the invention is that certain genes are over-expressed in the eyes of humans with AMD (e.g., see specification at page 21, lines 28-30, and at page 31, lines 4-9). To make this discovery, Applicants obtained RNA from postmortem eyes of normal and AMD-affected human subjects and compared patterns of gene expression using a novel gene expression macroarray technique called "CHANGE" (described, for example, on pages 19-21 and in further detail in Example 1, page 56, line 20 bridging page 57, line 13). See, for instance, the specification at page 20, line 15 bridging p. 21, line 25, which states in pertinent part:

To obtain genes of interest by differential expression, as further described in the examples below, a custom expression profiling strategy was developed, termed CHANGE (for Comparative Hybridization Analysis of Gene Expression). The CHANGE array included approximately 10,000 genes expressed in the RPE, arrayed in panels each comprising 96 cDNAs. (See FIG. 1.) To obtain phagogenes, the CHANGE array of RPE-expressed genes was screened with pairs of "+/- OS" hybridization probes made from total RNA expressed in a phagocytic RPE cell line during OS phagocytosis in vitro (+ OS probe) and in control cells without feeding of OS (- OS probe)..... To obtain AMD-related genes, the CHANGE array of 10,000 RPE-expressed genes was iteratively screened, as described above, using other pairs of "+/-" probes. The +/- probes used to identify AMD-related genes were made from total RNA extracted from the RPE/choroid of AMD-affected and unaffected human donor eyes, and from age-matched normal and affected eyes from a monkey model of AMD. Genes in the array were selected for further analysis based upon a showing of differential (i.e., increased or decreased) expression in AMD relative to aged normal control eyes. Based on the criterion of altered gene expression detected by CHANGE, approximately 200 AMD-related genes were identified.

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To identify AMD-related phagogenes ("AMDP genes"), the data from the above-described two CHANGE screenings were compared, to identify a subset of RPE genes differentially expressed both in OS phagocytosis by RPE cells and in AMD. As described above, the phagocytosis CHANGE screening yielded approximately 60 phagogenes and the putative AMD-related genes numbered approximately 200. Initial comparison of the two databases yielded a subset of 6 genes showing changed expression in both phagocytosis and AMD (Table 2). These genes are herein designated "AMD-related phagogenes" or "AMD/phagogenes," abbreviated to "AMDP." (Emphasis added.)

Thus, by using the CHANGE analysis, Applicants first discovered that the AMDP gene-of-interest that is the subject of the present application, i.e, MT1-MMP, is over-expressed in eyes of human subjects with AMD. Following on from this discovery, ("Additional studies of MT1-MMP provided evidence that overexpression of this gene is a common feature of at least one form of hereditary retinal degeneration besides AMD in which the primary pathology is in the RPE, i.e., that of the Royal College of Surgeons (RCS) rat...;" page 54, lines 9-12)), Applicants sought to test therapeutic agents that could counteract the destruction caused by the over-expression of the MT1-MMP. For this purpose, they chose a convenient small animal model, the RCS rat, which they discovered also over-expresses this gene during the course of the retinal degeneration (p. 54, lines 15-16). As described above, Applicants also discovered that MT1-MMP is over-expressed in the above-described large animal (monkey) model of AMD. Applicants then showed that intraocular injection of an antibody directed against MT1-MMP slowed the retinal degeneration in the RCS model.

As mentioned, the Office Actions alleges that "Applicant has only disclosed injecting an MT1-MMP antibody subretinally into the eyes of an RCS rat" and has not disclosed "a method of delaying a retinal degeneration in a subject as broadly claimed...." Applicants respectfully traverse this statement. Applicants have demonstrated over-expression of MT1-MMP in retina and RPE/choroid of human eyes

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with AMD, in a monkey model of AMD, and in the RCS rat, as well as having shown the delay/reversal of retinal degeneration in the rat model of MT1-MMP over-expression. Additionally, as was shown in an exhibit during the Interview, Applicants have now reduced to practice a double transgenic mouse model of AMD that conditionally overexpresses MT1-MMP upon administration of doxycycline. This mouse model of AMD was constructed as described in Example 7 (page 69, line 23 bridging page 70, line 18). As demonstrated in the Interview, a double transgenic mouse with a normal retina, upon induction of MT1-MMP overexpression by administration of doxycycline, develops retinal pathology that closely resembles that of the naturally-occurring monkey model of AMD (for which the causative gene is presently unknown).

Applicants have not tested therapeutic agents that can decrease the expression or activity of MT1-MMP in human mammalian subjects because at least in the United States, it is not lawful to test candidate drugs in humans before their safety and efficacy have been established in animals. However, the evidence of overexpression of this gene in retinal degeneration or AMD exhibited in four different species including humans, and demonstration of slowing of a retinal degeneration using a specific inhibitor of MT1-MMP in animal model exhibiting such overexpression of MT1-MMP provide strong evidence for the utility of the present invention and a strong rationale for further clinical testing of MT1-MMP-based therapeutics for these disorders.

Based on the foregoing remarks, Applicants respectfully submit that the specification as filed contains abundant written description in support of the recitations of claims 58 and 60 as presented herein. Because these claims do not contain new matter and because the inventors were in possession of the invention as claimed, withdrawal of the 35 USC § 112, first paragraph rejection, as outlined in section D of the Office Action, is respectfully requested.

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Rejection Under 35 USC § 102:

Claims 1-13, 15-17, 53, 57-58 and 60 stand rejected under 35 USC § 102 (b) as anticipated by U.S. Patent application publication 2003/0199440 ("440 publication"), as evidenced by U.S. Patent application publication 2005/0059595 ("595 publication").

According to the Office Action (p. 6), the '440 publication anticipates the claimed invention by teaching a method of treating AMD by administering an antibody specific for MT1-MMP, and that said treatment inhibits the specific proteolytic degradation effects of MMP14 (i.e., an activity of MMP14). Applicants strongly disagree.

A claim is anticipated only if each and every element as set forth in the claim is found either expressly or inherently described, in a single prior art reference. MPEP §2131. Applicants respectfully submit that the disclosure of the the '440 publication neither anticipates nor renders obvious Applicants' invention as presently claimed.

As amended herein, Claim 1 recites:

1. A method for treating a mammalian subject having, or at risk of developing, a retinal or choroidal degenerative disease or condition that is associated with increased expression of matrix metalloproteinase, membrane-associated 1 (MT1-MMP), the method comprising diagnosing said subject with, or at risk of developing, said retinal or choroidal degenerative disease or condition, and contacting a retinal or choroidal cell of said subject with an agent that decreases the expression of an AMDP-related or phagocytosis-related gene or protein, or decreases the activity of an AMDP-related or phagocytosis-related protein, wherein said AMDP-related or phagocytosis-related gene or protein is MT1-MMP, thereby treating said disease or condition. (Emphasis added.)

The '440 publication does not anticipate the method as claimed in Claim 1 as amended herein, and claims dependent thereon because, *inter alia*, the '440 publication does not teach or suggest the steps of diagnosing a mammalian subject with or at risk of developing a degenerative retinal or choroidal disease or condition that is associated

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with increased expression of MT1-MMP. Furthermore, the '440 publication does not teach or suggest treating a degenerative retinal or choroidal disease or condition by contacting a retinal or choroidal cell of a subject with an agent that decreases the expression or activity of a MT1-MMP gene or protein. As discussed in Applicants' previous response, the '440 publication merely provides generic description of a method of treatment involving an "inhibitor agent [that] can inhibit the action of at least one specific adverse protein (e.g., a specific protease)" that is "upregulated in a damaged tissue, such as a wound environment." The '440 publication does not teach or suggest that any specific "adverse protease" is overexpressed in any eye disease. Based on the disclosure in the '440 reference, one of ordinary skill in the art would not have had even a hint of a suggestion to diagnose a subject with a degenerative retinal or choroidal disease or condition associated with increased expression of MT1-MMP and, hence, to treat the subject's disease or condition with an agent that decreases the expression/activity of an MT1-MMP gene or protein because it was not taught or even suggested that MT1-MMP is overexpressed in such diseases of the eye. That is Applicants' discovery.

In the Office Actions dated 10/21/05, and 05/16/06, the Examiner states that "the '440 patent application teaches a method for treatment of damaged tissues associated with age-related macular degeneration (AMD) by administering an inhibitor of adverse proteases (see paragraph 216-218, and claim 11)...The specification of the '440 patent application further discloses that said inhibitor can be specific for MMP14 (see paragraph 222)." In response to Applicants' arguments filed 02/21/06, the Office Action further states that "the '440 application teaches a method of treating AMD by administering an antibody specific for MT1-MMP, and that said treatment inhibits the specific proteolytic degradation effects of MMP14 (i.e. an activity of MMP 14). Since MMP14 is an AMD-related gene ...the reference does anticipate the instant invention."

Applicants respectfully submit that the Office Action does not point to any specific passages of the '440 reference that support many of the elements of the presently claimed invention. For example, contrary to the above-quoted assertion in the Office Action, Applicants are unable to find any disclosure of an antibody that specifically binds to a MT1-MMP (MMP14) protein or peptide, as claimed in Claim 15, an antibody that

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neutralizes at least one biological activity of MT1-MMP, as claimed in Claim 16, or of use of any specific inhibitor of any "adverse protease" as a treatment for retinal or choroidal degenerations or AMD, as claimed in Claims 1 and 4. Rather, Applicants respectfully submit that the purported anticipation of claims 1-13, 15-17, 53, 57-58 and 60 by the '440 publication is the product of impermissible picking and choosing of the various elements of the instant claims from among large-to-vast Markush groups that appear in several disjointed passages of the '440 reference.

According to MPEP § 2131.02, a claimed product can be anticipated by a prior art reference even if it is necessary to select portions of the reference and combine them so long as the classes from which the selections are made are "sufficiently limited or well delineated." Citing Ex parte A, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990) and In re Petering, 301 F.2d 676, 133 USPQ 275 (CCPA 1962), this section of the MPEP states as follows:

When the compound is not specifically named, but instead it is necessary to select portions of teachings within a reference and combine them, e.g., select various substituents from a list of alternatives given for placement at specific sites on a generic chemical formula to arrive at a specific composition, anticipation can only be found if the classes of substituents are sufficiently limited or well delineated. Ex parte A, 17 USPQ2d 1716 (Bd. Pat. App. & Inter. 1990). If one of ordinary skill in the art is able to "at once envisage" the specific compound within the generic chemical formula, the compound is anticipated. One of ordinary skill in the art must be able to draw the structural formula or write the name of each of the compounds included in the generic formula before any of the compounds can be "at once envisaged." One may look to the preferred embodiments to determine which compounds can be anticipated. In re Petering, 301 F.2d 676, 133 USPQ 275 (CCPA 1962).

The '440 publication provides no teaching that any of its disclosed compositions are effective to treat any eye disease or condition. To arrive at the combination of even

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three of the elements of the invention as claimed, for example, in Claim 1 of the instant application, (i.e., "retinal or choroidal degenerative disease or condition"; "increased expression of MT1-MMP"; and "agent that decreases expression or activity of MT1-MMP,"), the person of ordinary skill in the art reading the '440 application, provided with no specific guidance, preferred compositions or preferred clinical applications (other than "chronic dermal ulcers" ('440, paragraph 0003)), would have been required to select: 1) a retinal degenerative disease (AMD) from a list of 18 broad classes of diseases disclosed in paragraph 0218; 2) MT1-MMP/MMP14 from a list of 19 different disclosed "adverse proteases" of the MMP class ('440, paragraph 0308); and 3) an inhibitory agent from a list of untested small molecule compounds numbering in the thousands ('440, paragraphs 0669-3201), in addition to other types of generically described inhibitors, such as antibodies ('440, paragraph 0309). In view of the many thousands of possible combinations of diseases, adverse proteases and alleged inhibitory agents of such proteases disclosed in the '440 publication, one of ordinary skill in the art would clearly have been unable to "at once envisage" the method of treatment as instantly claimed in Claim 1, and claims dependent thereon. This is done in the Office Action only after using the presently claimed invention as a road map. Furthermore, these deficiencies in the '440 application are not remedied by the '595 post-filing reference relied on by the Examiner to support a rejection of claims 9, 12, 58, and 60.

In summary, for the reasons previously of record and presented herein, Applicants submit that the invention as presently claimed is not anticipated or rendered obvious by the cited '440 reference, either alone or in combination with the '595 reference. Accordingly, reconsideration and withdrawal of the rejection of Claim 1, and claims dependent thereon, under 35 USC § 102 is respectfully requested.

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CONCLUSION:

In view of the amendments and arguments presented herein, Applicants believe the pending application is in condition for allowance. Early and favorable action on the application is respectfully requested. If the Examiner believes an interview would expedite prosecution to allowance, the Examiner is cordially invited to call the undersigned at the number indicated.

Dated: November 7, 2006

Respectfully submitted,

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